Tuberculosis Recurrence: Multivariate Analysis of Serum Levels of Tuberculosis Drugs, Human Immunodeficiency Virus Status, and Other Risk Factors

Masahiro Narita,[1–3] Michie Hisada,[4] Brinda Thimmappa,[4] Jerry J. Stambaugh,[1] Emad Ibrahim,[1] Elena S. Hollender,[1,2] and David Ashkin[1–3]

[1]A. G. Holley State Tuberculosis Hospital, Lantana, [2]Florida Bureau of Tuberculosis Control and Prevention, Florida Department of Health, Tallahassee, and [3]Division of Pulmonary and Critical Care, University of Miami School of Medicine, Miami; and [4]Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

We examined risk factors for tuberculosis recurrence in patients admitted to a tuberculosis hospital in Florida in 1996 and 1997. Recurrence of tuberculosis was not significantly associated with tuberculosis drug levels or HIV status, which indicates that routine drug monitoring may not be beneficial in general patient management.

Short-course chemotherapy with isoniazid, rifampin, and pyrazinamide is the standard treatment of tuberculosis [1]. However, recurrence occurs in 2.4%–5.5% of cases, even when the patient receives directly observed therapy [2]. Poor compliance accounts for most treatment failures and subsequent relapses, but other possible risk factors may include HIV coinfection, suboptimal serum levels of tuberculosis drugs, preexisting drug resistance of *Mycobacterium tuberculosis,* and silica dust exposure [3–5]. Identifying patients at high risk of tuberculosis recurrence is critical, because these patients may require intensified and/or prolonged treatment and closer posttreatment surveillance. To address this issue, we analyzed the characteristics of patients with tuberculosis who were admitted to A. G. Holley State Hospital, a specialized tuberculosis treatment facility in Florida.

Methods. A total of 193 patients with culture-proven tuberculosis who were sequentially admitted to A. G. Holley State Hospital from 1 January 1996 through 31 December 1997 were examined. Tuberculosis recurrence was defined as new disease proven by means of culture to be due to *M. tuberculosis* in persons who had been microbiologically disease free for at least 3 months after 6 months of directly observed therapy. Standard therapy for pulmonary tuberculosis consisted of isoniazid and rifampin with pyrazinamide for the first 2 months of therapy, as recommended by the Centers for Disease Control and Prevention and American Thoracic Society [6]. Demographic and clinical data for all patients were collected through medical record abstraction. Occupational history was determined through a standardized interview. Data on serum isoniazid and rifampin levels were available for approximately half of the patients; blood was drawn 2 and 6 h after the administration of the oral dose of medications at least 2 weeks after initiation of therapy, when stable (steady state) drug levels were expected.

Susceptibility testing of *M. tuberculosis* for the first-line tuberculosis medications was done at Florida State Laboratory (Jacksonville). Multidrug-resistant (MDR) tuberculosis was diagnosed when the *M. tuberculosis* isolate was resistant to both isoniazid and rifampin. Drug concentration was measured by means of high performance liquid chromatography (National Jewish Medical and Research Center, Denver).

HIV antibodies were analyzed by means of ELISA and confirmed by means of Western blot assay. For HIV-positive patients, CD4 cell counts were measured by means of flow cytometry. The HIV RNA load was quantified by use of PCR.

Five patients with a history of MDR tuberculosis from previous admissions were excluded from this analysis. Characteristics of patients with tuberculosis recurrence and those without recurrence were compared. Exposure to silica dust, presence of MDR tuberculosis, and HIV infection were determined on the current admission and were dichotomized. Patients were categorized according to race as white, black, Asian, or Hispanic. CD4 cell count (<100 cells/mL vs. ⩾100 cells/mL) and HIV RNA load (<150,000 copies/mL vs. ⩾150,000 copies/mL) were dichotomized at the median as "higher" versus "lower" levels. Age was a continuous variable. Serum drug levels at steady state were dichotomized at the lower limit of their dose-specific expected ranges, by use of data from healthy volunteers: <3 mg/mL versus ⩾3 mg/mL, for patients receiving isoniazid at 300 mg daily; <9 mg/mL versus ⩾9 mg/mL, for those receiving isoniazid at 900 mg twice weekly; and <8 mg/mL versus ⩾8 mg/mL, for those receiving rifampin at 600 mg daily [7].

The mean age, serum drug level, CD4 cell count, and HIV

Received 14 February 2000; revised 23 June 2000; electronically published 25 January 2001.

Reprints or correspondence: Dr. David Ashkin, A. G. Holley State Tuberculosis Hospital, 1199 West Lantana Rd., Lantana, FL 33462 (David_Ashkin@doh.state.fl.us).

Clinical Infectious Diseases 2001; 32:515–7

1058-4838/2001/3203-0027$03.00

RNA load by recurrence status were compared by use of the Wilcoxon rank sum test. Sex distribution, silica dust exposure, presence of MDR tuberculosis, and HIV status between the 2 groups were compared by use of the Student's *t* test. The ORs and 95% CIs for tuberculosis recurrence were estimated by use of logistic regression models with use of the SAS statistical package (SAS Institute). *P* values were 2-sided.

Results. A total of 188 patients (133 men and 50 women) were included in the analysis. The mean age was 43 years (range, 22–80 years). The mean interval between the preceding and current tuberculosis treatment was 2.1 years (range, 1–8 years). One hundred eleven (59%) were black, 64 (34%) were white, 12 (6%) were Hispanic, and 1 (<1%) was Asian. Thirty-seven (20%) had a history of unprotected occupational exposure to silica dust. MDR tuberculosis was present in 18 patients (10%), all of whom had a history of noncompliance with therapy. Sixty-nine patients (37%) were infected with HIV; these 69 patients had a mean CD4 cell count and HIV RNA load of 165 cells/mL (range, 2–1203 cells/mL) and 706,368 copies/mL (range, <400–8,007,483 copies/mL), respectively. Twenty-eight (15%) of the 188 patients had a confirmed history of injection drug use. Twenty-five (13%) had tuberculosis recurrence diagnosed despite prior completion of directly observed therapy.

Both patients who had and those who didn't have tuberculosis recurrence were similar with respect to age, sex, and race. There was no significant difference in the prevalence of exposure to silica dust (28% vs. 18%; $P = .26$), MDR tuberculosis (12% vs. 9%; $P = .66$), HIV infection (28% vs. 38%; $P = .33$), or history of injection drug use (21% vs. 16%; $P = .60$) across the 2 groups. Moreover, no significant differences were found in tuberculosis recurrence on the basis of drug levels or dosages. Serum levels of tuberculosis drugs were not significantly lower among patients with MDR tuberculosis than among those without MDR tuberculosis.

Univariate logistic regression analysis showed that neither age (OR, 0.97 per 10-year increase; 95% CI, 0.67–1.5), sex (OR, 2.1 for men; 95% CI, 0.67–6.3), nor race (OR, 1.3 for black compared with all others; 95% CI, 0.53–3.0) was associated with a risk of tuberculosis recurrence. HIV infection (OR, 0.63; 95% CI, 0.25–1.6), silica dust exposure (OR, 1.7; 95% CI, 0.66–4.5), presence of MDR tuberculosis (OR, 1.3; 95% CI, 0.36–5.0), and injection drug use (OR, 1.3; 95% CI, 0.45–4.0) were also not associated with a risk of tuberculosis recurrence. The probability of tuberculosis recurrence was not significantly associated with lower-than-expected serum drug levels (OR, 0.88; 95% CI, 0.34–2.3 for isoniazid; OR, 2.7; 95% CI, 0.70–10.2 for rifampin).

Among HIV-infected patients, a CD4 cell count <100 cells/mL (OR, 2.7; 95% CI, 0.48–14.9) and an HIV RNA load ⩾150,000 copies/mL (OR, 1.3; 95% CI, 0.27–6.5) were not significantly associated with tuberculosis recurrence. The presence of MDR *M. tuberculosis* was 4 times more likely among HIV-positive patients who experienced tuberculosis recurrence (OR, 4.1; 95% CI, 0.48–36.0; table 1). HIV-positive men were at an elevated risk of recurrence compared with HIV-positive women (OR, 6.1; 95% CI, 0.48–36.0). This association was slightly attenuated after adjustment for history of injection drug use (OR, 5.8; 95% CI, 0.68–50.2).

Discussion. How serum tuberculosis drug levels have been a factor in the outcome of tuberculosis disease has been a matter of debate, and as yet there are no clear data regarding this association. Existing findings on the association of tuberculosis recurrence with other presumed risk factors (e.g., silica dust exposure and HIV infection) have also been inconsistent [3, 5, 8, 9]. We examined the association of tuberculosis drug levels, silica dust exposure, and HIV status with the risk of tuberculosis recurrence in a large number of patients. As other studies have found [5, 7], a large percentage of patients (60%) had lower-than-expected levels of isoniazid or rifampin, which raises the concern that the expected drug levels derived from healthy volunteers may not represent the therapeutic range among patients with tuberculosis. Our analysis showed that the risk of tuberculosis recurrence was not associated with drug levels; this suggests that close monitoring of drug levels may not be beneficial in general clinical settings.

All patients who relapsed with MDR tuberculosis had a previous history of noncompliance with therapy, and tuberculosis drug levels were not found to be lower among patients with MDR tuberculosis than among those without MDR tuberculosis. Therefore, the development of MDR tuberculosis in our patients appears to be due, in large part, to nonadherence to therapy rather than to low drug levels. In cases of MDR tuberculosis, distinguishing new infection with an MDR *M. tuberculosis* strain from a "relapse" with evolution of the initial

Table 1. Adjusted odds ratios for tuberculosis recurrence among 69 HIV-positive patients admitted to A. G. Holley State Hospital, Florida, 1996–1997.

Model, variables	OR (95% CI)
A	
Age, per 10-year increase	0.47 (0.13–1.7)
Male sex	3.7 (0.56–25.1)
Multidrug-resistant tuberculosis	4.0 (0.54–29.2)
B	
Age, per 10-year increase	0.39 (0.09–1.8)
Male sex	6.1 (0.76–49.0)
Multidrug-resistant tuberculosis	4.1 (0.48–36.0)
Low CD4 cell count (<100 cells/mL)	2.7 (0.42–17.6)
High HIV RNA load (⩾150,000 copies/mL)	0.89 (0.14–5.8)

NOTE. Logistic regression model adjusts for all variables shown. Referent categories are female sex, absence of multidrug-resistant tuberculosis, a CD4 cell count ⩾100 cells/mL, and an HIV RNA load <150,000 copies/mL.

strain into an MDR strain requires molecular analysis by means of restriction fragment length polymorphisms. This was not analyzed, however, because the specimens from the initial episodes were not available for comparison for the majority of the patients.

The lack of association of tuberculosis recurrence with HIV status in this study lends support to the current guidelines of the Centers for Disease Control and Prevention, which recommend an identical 6-month course of therapy for patients both with and without HIV infection [6]. There was an indication that the presence of MDR tuberculosis was associated with tuberculosis recurrence among HIV-positive patients. Although this association was not statistically significant, it is prudent for clinicians to look for an MDR *M. tuberculosis* strain when an HIV-infected patient presents with recurrence of tuberculosis. We also found that HIV-positive men are at a 6-fold greater risk of tuberculosis recurrence than are HIV-positive women. The higher risk of tuberculosis recurrence in these men may reflect the presence of other risk behaviors closely related to HIV infection. However, additional adjustment for injection drug use did not entirely explain the elevated risk among men. Because the analysis was done on a limited number of HIV-positive patients, caution is needed in the interpretation of these data.

In conclusion, neither serum tuberculosis drug levels, HIV status, nor silica dust exposure appear to be strong determinants for the risk of tuberculosis recurrence among our patients. Other factors unavailable for evaluation in this study, such as mycobacterial burden before initial tuberculosis therapy and serum tuberculosis drug levels during the first treatment, may have an as yet undetermined role. Although absolute risk factors for tuberculosis relapse remain to be defined, it does not appear that tuberculosis drug levels play a significant role. This finding supports the position that the routine monitoring of tuberculosis drug levels is not beneficial in tuberculosis case management.

References

1. Centers of Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR Morb Mortal Wkly Rep **1998**; 47(RR-20):1–58.
2. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med **1994**; 330:1179–84.
3. Pulido F, Pena J, Rubio R, et al. Relapse of tuberculosis after treatment in human immunodeficiency virus–infected patients. Arch Intern Med **1997**; 157:227–32.
4. Kimerling ME, Phillips P, Patterson P, et al. Low serum antimycobacterial drug levels in non-HIV infected tuberculosis patients. Chest **1998**; 113: 1178–83.
5. Hong Kong Chest Service/Tuberculosis Research Center, Madras/British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. Am Rev Respir Dis **1991**; 143: 262–7.
6. American Thoracic Society/Centers for Disease Control and Prevention. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med **1994**; 149:1359–74.
7. Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. Clin Chest Med **1997**; 18:79–87.
8. Hnizdo E, Murray J. Risk of pulmonary tuberculosis relative to silicosis and exposure to silica dust in South African Gold Miners. Occup Environ Med **1998**; 55:496–502.
9. Schluger NW. Issues in the treatment of active tuberculosis in human immunodeficiency virus–infected patients. Clin Infect Dis **1999**; 28: 130–5.